Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Heart Failure with Reduced Ejection Fraction (HFrEF)***

-May 2022-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of all agents recommended in patients with heart failure with reduced ejection fraction (HFrEF) by the 2022 American Heart Association (AHA) and American College of Cardiology (ACC) guidelines published in April 2022.[1] These agents include beta-blockers (bisoprolol, metoprolol succinate, and carvedilol only), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin-neprilysin receptor inhibitors (ARNis), mineralocorticoid receptor agonists (MRAs), sodium-glucose transport protein 2 inhibitors (SGLT2i), soluble guanylate cyclase inhibitors (digoxin, vericiguat), and ivabradine. Loop diuretics are discussed in the heart failure with preserved ejection fraction formulary brief. Following clinical review and analysis, the NPTC **added sacubitril-valsartan and named both formulations of metoprolol (tartrate AND succinate)** to the National Core Formulary.

Discussion:

Heart failure is a common disease with increasing prevalence in the United States (US) over the last decade.[2] American Indian and Alaska Native (AI/AN) people die from cardiovascular (CV) disease more than any other racial group in the US.[2] Disproportionately high rates of comorbidities in AI/AN populations such as type II diabetes mellitus (DM) and hypertension increase the risk of heart failure. While data on rates of HFrEF in AI/AN population is limited, it is likely to be underdiagnosed and under-treated in these populations.[2] The Strong Heart Study identified that in AI/AN population non-insulin dependent DM is an independent risk factor for increased risk of adverse cardiac effects outside of obesity and increased arterial pressure supporting the need for early diagnosis and readily available evidence-based therapies.[3]

HFrEF is currently classified by the AHA/ACC as an ejection fraction (EF) ≤ 40%.[1] Diagnosis of HFrEF relies on echocardiogram to determine EF as well as measurements of serum pro-NT-BNP and BNP for monitoring. Guideline Directed Medical Therapy (GDMT) represents a comprehensive diagnostic approach with lifestyle, pharmacologic and procedural interventions to improve morbidity and mortality from HFrEF. GDMT as it relates to pharmacologic interventions relies on four pillars of treatment recommended for all patients with an EF ≤ 40% including a beta-blocker (BB), an ARNi, a MRA, and a SGLT2i. The number of patients needed to treat (NNT) to prevent one death is staggering for each individual pillar: ARNi (NNT=27), ACEi/ARB (NNT=26), beta-blocker (NNT=9), MRA (NNT=6), and SGLT2i (NNT=22).[1] While these pharmacologic pillars are essential to guideline directed care of the HFrEF patient, non-pharmacologic therapies and lifestyle recommendations are of great importance and all readers are encouraged to consult the recently published AHA/ACC guidelines for comprehensive details of pharmacologic therapy including initiation, and monitoring.

Beta-blockers have demonstrated high clinical efficacy for reduction of morbidity and mortality in HFrEF and are recommended by the AHA/ACC guidelines with a classification of recommendation of 1 (*highly recommended, benefits greatly outweighing risks*) and level of evidence of A (*high quality evidence with more than 1 randomized controlled trial (RCT)*)[1]. The AHA/ACC considers BB to be of high economic value. The COMET trial in 2003 demonstrated superiority of survival in HFrEF of carvedilol over metoprolol tartrate.[11] In 2018, a retrospective study of VA patients demonstrated a mortality benefit for carvedilol over metoprolol succinate.[12] Unfortunately no head to head trial of metoprolol tartrate versus succinate exists, however the AHA/ACC guidelines specifically recommend metoprolol succinate for the treatment of HFrEF.

Mineralocorticoid receptor agonists (MRAs), spironolactone and epleronone, are the second pillar of GDMT for HFrEF. Again, little new data has emerged to support these agents in treatment, however the structure of the AHA/ACC recommendations now highlights these as a standard part of GMDT without a preference of either agent. MRA therapy is recommended as a 1A, and is considered to have high economic value by the AHA/ACC.

The 2022 AHA/ACC guidelines brought significant change to ACEi/ARB's role in HFrEF therapy: they are now second line to a new class of medications called ARNis. ARNis are a relatively new class of medication, of which only one formulation is available in the United States, sacubitril-valsartan (Entresto®). The 2014 PARADIGM-HF trial demonstrated decreased deaths from CV causes and hospitalizations from HFrEF with ARNi (21.8% vs. 26.5%, with a hazard ratio (HR) of 0.80).[5] A more recent meta-analysis comparing any ACEi/ARB to sacubitril-valsartan demonstrated 23 fewer deaths per 1000 people treated with ARNI[6]. In 2017, the AHA recommended ACEi/ARB for treatment of HFrEF and if these were tolerated, then consideration of an ARNi to reduce morbidity and mortality, however in the 2022 updated guidelines, an ARNi is recommended as first line to reduce morbidity and mortality in HFrEF patients: "In patients with chronic symptomatic

HFrEF, treatment with an ARNi instead of an ACEi provides high economic value".[1] In a meta-analysis exploring cost efficacy of an ARNi vs. ARB, it was estimated that in the US that 52,856 fewer heart failure admissions would occur per year if all qualifying inpatients were prescribed sacubitril-valsartan prior to discharge compared with enalapril.[10] Compellingly, the US Department of Veterans Affairs placed sacubitril-valsartan on their national formulary in February 2022 preceding the new AHA/ACC guidelines due to the exceptional clinical benefits and high economic value.

The SGLT2i agent, empagliflozin, was added to the IHS National Core Formulary in 2019 following a review of DM, however data now supports the use of both empagliflozin and dapagliflozin in GDMT to reduce morbidity and mortality in HFrEF. In the EMPEROR-Reduced trial, the reported NNT was 19 for empagliflozin to prevent one death vs. placebo.[7] In the DAPA-HF trial, the NNT=21 for dapagliflozin vs. placebo.[8] No head to head comparator trials exist for HFrEF patients. The addition of SGLT2i to the AHA/ACC guidelines as a part of GDMT occurred in 2022 and is considered a 1A recommendation and provides intermediate economic value.

Several other agents including vericiguat, digoxin, and ivabradine were reviewed. These medications may play an important role in special populations with HFrEF, but are not currently included in the GDMT recommendations by the AHA/ACC. New data exists supporting the use of vericiguat with a trend toward improvement CV death and HF hospitalizations, but with increased side effects, and thus is not currently part of GMDT for treatment of HFrEF.

An extremely compelling meta-analysis done in 2022 demonstrated that use of GDMT (defined as use of an ARNi, MRA, beta blocker and SGLT2i) in HFrEF patients, can extend life expectancy by 7.9 years in a 50-year old and by 5.0 years in a 70-year old.[9] Further demonstrating the profound and direct clinical impact that the availability of these medications will have on the IHS patient population.

Findings:

In 2022, the AHA/ACC restructured their guidelines to include a four-pillar approach to the treatment of HFrEF, termed GDMT, which includes four core therapeutic agents: BB, ARNi, MRA, and SGLT2i. After review of current data, the NPTC found compelling evidence that all four of these agents represent standard of care, substantially improved morbidity and mortality, addressed a specific and important health disparity for AI/AN patients, and enhanced critical access to the pharmacy benefits of the IHS. Thus, the NPTC **added sacubitril-valsartan and named both formulations of metoprolol (tartrate AND succinate)** to the National Core Formulary.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:

1. Heidenreich PA, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e895-e1032.
2. Breathett Ket. al; on behalf of the American Heart Association Council on Epidemiology and Prevention; Council on Quality of Care and Outcomes Research; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Lifestyle and Cardiometabolic Health. Cardiovascular health in American Indians and Alaska Natives: a scientific statement from the American Heart Association. Circulation. 2020;141: e948–e959.
3. Devereux RB, et al. Impact of Diabetes on Cardiac Structure and Function: The Strong Heart Study. Circulation. 2000;101: 2271–2276.
4. Townsend, R. Major Side effects of angiotensin-converting inhibitors and angiotensin II receptor blockers. UpToDate, March 2022. Accessed April 2022.
5. McMurray, JJV, et al. Angiontensin-Neprilysin Inhibition versus Enalapril in Heart Failure. NEJM. 2014; 371:993-1004.
6. Nielsen, EE, et al. Beneficial and harmful effects of sacubitril/valsartan in patients with heart failure: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Open Heart 2020;7:e001294.
7. Packer, M, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. NEJM. 2020; 383:1413-24.
8. McMurray, JJV, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. NEJM. 2019; 381:1995-2008.
9. Tromp J, et al. A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction. J Am Coll Cardiol HF. 2022; 10:(2):73–84.
10. Gaziano et al. Cost-effectiveness of Sacubitril-Valsartan in Hospitalized patients who have heart failure with reduced ejection fraction. JAMA Cardiol. 2020; 5(11):1236-44.
11. Poole-Wilson, PA, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomized controlled trial. Lancet. 2003; 5;362(9377):7-13.
12. Ajam, T, et al. Effect of carvedilol vs metoprolol succinate on mortality in heart failure with reduced ejection fraction. 2018;199:1-6.